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The prognostic value of long non-coding RNA MEG3 expression in the survival of cancer patients: A meta-analysis

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Abstract

Long non-coding RNAs (lncRNAs) play an important role in carcinogenesis and cancer progression. lncRNA MEG3 is a tumor suppressor that is down-regulated in several cancers. However, its prognostic value in human malignancies remains controversial. We have therefore undertaken a meta-analysis to explore the relationship between cancer survival and the expression of long non-coding RNA MEG3. A systematic literature search identified 13 potentially eligible investigations comprising 1733 patients in nine different cancer types. In the pooled analysis, a low expression of MEG3 was associated with a low overall survival (OS) in cancer patients with a combined HR of 0.830 [hazard ratio (HR) =0.83; 95% CI: 0.70–0.98; P=0.003; random effect model]. However, sub-group analysis according to cancer type revealed that MEG3 expression was not associated with better OS in gastrointestinal cancer (HR = 0.58, 95% CI = 0.33 to 1.03, P = 0.06) and breast cancer patients (HR = 0.85, 95% CI: 0.12 to 5.88, P = 0.87). In conclusion, our results demonstrate that only in the pooled analysis, there was a significant relationship between MEG3 expression and cancer survival. Further investigation of other molecular biomarkers involved in tumorigenesis-related pathways is necessary.

Keywords: lncRNAs, Maternally expressed gene 3, Tumor survival

Introduction

Cancer is one of the **most** prevalent causes of mortality, globally. **Despite** improvements **in** modern treatments such as surgery, radiotherapy, chemotherapy, and the combination therapy, long-term survival rate and quality of life remain poor **for patients with** advanced stages of **cancer** (Bahrami et al., 2017a). **Therefore, improving therapeutic efficacy and patient outcome requires a better understanding of the molecular mechanisms contributing to the pathogenesis of these cancers, and the identification of new drug targets and novel therapeutics** (Bahrami et al., 2017b). Genome-wide studies and high throughput transcriptome analysis have demonstrated that the human genome contains nearly 20,000 protein-coding reading frames that constitutes less than 2% of the total genome. **However,** non-coding transcripts such as short or long noncoding RNAs (lncRNAs) **comprise more than** 98% of **the** human genome (Louro et al., 2009; Lv et al., 2016).

lncRNA is a RNA molecule of >200 bases in length and often **plays** important roles in biological processes that include gene expression, transcription, cellular development, differentiation, proliferation, **and** cell fate. **Moreover, lncRNAs have** a large number of potential functions, such as **being markers of** reprogramming stem cell pluripotency, parental imprinting, and regulation of eukaryotic genome and epigenome (Loewer et al., 2010; Louro et al., 2009; Mercer et al., 2009; Wilusz et al., 2009). lncRNAs can be **viewed** as potential tumorigenic and anti-tumorigenic RNAs (Huarte and Rinn, 2010). Dysregulation of several lncRNAs has been found to be **associated with** cancer cell proliferation, development, migration, invasiveness (Lin et al., 2007; Liu et al., 2012; Ma et al., 2014), metastasis, recurrence, and prognosis of tumors (Liao et al., 2017; Tuo et al., 2015).

The maternally expressed gene 3 (MEG3) lncRNA is an imprinted gene, amplified from the **maternally-derived allele, is approximately** 1.6 kb nucleotides in length **and has been** mapped **to** chromosome 14q32. MEG3 can suppress tumor cell proliferation, or trigger apoptosis by stimulating p53-dependent transcription (Wang et al., 2012). Hypermethylation of the promoter or the intergenic region of MEG3 occurs in some human tumors and results in loss of MEG3 expression (Balik et al., 2013; Benetatos et al., 2011). **Abnormal** expression

of MEG3 **has** been found in several malignancies (Braconi et al., 2011; Lu et al., 2013; Qin et al., 2013; Ying et al., 2013) and **appears to contribute** to the pathogenesis of several cancers including hepatocellular carcinoma (HC) (Braconi et al., 2011), cervical cancer (CC) (Zhang et al., 2016b), non-small cell lung cancer (NSCLC) (Lu et al., 2013), bladder cancer (BC) (Ying et al., 2013), pituitary tumor (Chunharojrith et al., 2015) and gastric cancer (GC) (Yan et al., 2014). **However**, the prognostic value of MEG3 expression in cancer is unknown. **We therefore undertook** a quantitative meta-analysis to assess the association between low MEG3 expression with overall survival and prognosis in different cancer types.

Methods

Inclusion and exclusion criteria

A comprehensive search of PubMed, Web of Science, EMBASE, Scopus and the Cochrane library restricted to English language articles up to January 2018 was performed. The scientific search strategy encompassed the following format of key words: [(MEG3 OR long non-coding RNA MEG3 OR lncRNA MEG3 OR maternally expressed gene 3)] AND [(tumor OR cancer OR neoplasm OR carcinoma OR malignancy)] AND [(prognosis OR predict OR survival OR overall survival OR survival rate)]. We also manually checked the reference lists of selected articles and relevant reviews. Studies **of** association between MEG3 expression in tumor or blood specimens and prognosis of cancer patients that reported the survival outcomes as overall survival (OS) were eligible for full-text assessment. Exclusion criteria was review articles, letters, case reports, animal studies, irrelevant subjects, studies about other lncRNAs, and studies concerned **with** molecular structure of MEG3. When several articles reported similar data, the article with **a** larger population was selected. Two authors (M.M and A.B) independently reviewed the studies, and discrepancies were decided by consensus.

Data extraction and statistical methods

This information was extracted from each selected study: first author, publication year, site of cancer, sample size, and survival outcome [hazard ratio (HR) with 95% confidence intervals (CI)]. The results of multivariate Cox hazard regression analysis (HR with 95% CI) were applied for survival measurements. If data of interest were not directly accessible, the log-rank *p*-value and Kaplan–Meier survival curves were used for calculation according to the hierarchical series of steps defined by Parmar et al. (Parmar et al., 1998). A test of heterogeneity among combined HRs was performed using Cochran's *Q* test and Higgins *I*² statistic (Higgins and Thompson, 2002). A *p*-value of < 0.05 or *I*² > 50% was regarded statistically significant. A random effect model was used if heterogeneity was considerable; otherwise fixed model was used (DerSimonian and Laird, 1986). Publication bias was assessed by construction and visual evaluation of funnel plot symmetry and applying Egger's test when at least 10 articles were eligible with significance of < 0.05 (Terrin et al., 2003). Analysis was performed using comprehensive meta-analysis software version 2 (Biostat, Inc., Englewood, NJ) (Borenstein et al., 2005).

Results

Literature research

The literature search resulted in 362 studies (Figure 1). Of these, 286 publications were excluded because they failed to meet the eligibility criteria. We obtained full texts for the remaining 76 articles. Sixty-three publications were excluded because they were not human studies (*n* = 19), were duplicate publications (*n* = 12), were review articles (*n* = 7), or engaged other biomarkers (*n* = 25). Ultimately, 13 articles successfully fulfilled our pre-defined selection criteria for meta-analysis.

Study and patient characteristics

The thirteen studies were published between 2013 and 2017 and all of them were conducted in China. The number of subjects in these studies ranged from 44 to 257, and all

of the studies used the real-time reverse transcription-PCR (Rt-PCR) method to measure the expression level of lncRNAs MEG3 in tumor tissues. Among the studies, nine different tumor types were included in this meta-analysis, including digestive system carcinomas: one tongue squamous cell carcinoma (TSCC) (Jia et al., 2014), two esophageal squamous cell cancers (ESCC) (Dong et al., 2017; Lv et al., 2016), two colorectal cancer (CRC) (Li et al., 2017; Yin et al., 2015), one gastric cancer (GC) (Sun et al., 2014), and two hepatocellular carcinoma (HCC) (Yang et al., 2015; Zhuo et al., 2016); respiratory system carcinomas: one non-small cell lung cancers (NSCLC) (Lu et al., 2013); urinary system carcinoma: one gallbladder cancer (GBC) (Liu et al., 2016a); parenchymal tumor: two breast cancer (BC) (Shi et al., 2016; Zhang et al., 2016a) and bone tumor: one osteosarcoma (Tian et al., 2015). Detailed values from the studies are shown in Table 1.

Meta-analysis

In the pooled analysis of 13 eligible studies among 1733 cancer patients, a low expression of MEG3 was significantly associated with a poorer OS with a combined HR of 0.830 (HR 0.83; 95% CI: 0.70–0.98; $P=0.003$) (Figure 2.A). We found significant heterogeneity among studies on the association between MEG3 expression level and OS of patients [$I^2 = 67.5\%$; $Q = 36.9$; degrees of freedom (df) = 12; $P<0.001$]. Because of this, a random-effects model was used. The result of Egger's test ($p=0.004$) and following inspection of the symmetry of the funnel plot indicated no significant evidence of publication bias (Figure 2.B).

Next, we performed subgroup meta-analysis to investigate whether the heterogeneity is due to type of cancers. Eight studies provided an OS for GI cancer and two studies for BC. In the stratified analysis by cancer types, MEG3 expression was not associated with better OS of the GI cancer patients (HR = 0.58, 95% CI: 0.33 to 1.03, $P = 0.062$; Figure 3.A). Also in BC patients, MEG3 overexpression was not significantly associated with better OS (HR = 0.85, 95% CI: 0.12 to 5.88, $P = 0.87$; Figure 3.B)

Discussion

It is of interest to identify prognostic markers for cancer that can assist in risk stratification and facilitate clinical decision-making. Recently, there has been increasing evidence for the ectopic expression of lncRNAs, which suggests that these may be potential markers for prognosis in cancer patients (Chen et al., 2017; Huang et al., 2017a). Furthermore, functional studies indicate that lncRNAs may act as oncogenes or tumor suppressors in various cancers (Liu et al., 2016b; Shi et al., 2013; Wang et al., 2016a).

In recent years, much attention has been focused on identification of prognostic markers in cancer patients, with the objective of using this information to tailor treatment and improve survival (Kosari et al., 2008; Yamada et al., 2008; Zheng et al., 2013). lncRNA MEG3 is mutually imprinted with the paternally amplified gene DLK1 generating an imprinting region on human chr14 and on mouse chr12 (Wylie et al., 2000). In a previous meta-analysis on six lncRNAs, it was revealed that the expression of MEG3 is positively associated with OS in patients with NSCLC and might be a novel predictive factor for prognosis of these patients (Wang et al., 2016b). Dong et al. reported that down-regulation or hypermethylation of MEG3 was significantly associated with poorer overall survival in patients with ESCC (Dong et al., 2017). Moreover, Jia and colleagues introduced MEG3 and miR-26a as potential prognostic biomarkers for stratification of tongue squamous cell carcinoma patients, since their reduced expression was associated with poor prognostic outcomes (Jia et al., 2014). Similarly, Lu et al. found that NSCLC patients with lower levels of MEG3 expression had a relatively poor prognosis (Lu et al., 2013). Shi and colleagues conducted a study to clarify the clinical significance of MEG3 in BC and found that MEG3 expression is an independent prognostic factor for BC patients (Shi et al., 2016). Similar results were obtained for other types of cancer including gastric cancer (Sun et al., 2014), colorectal cancer (Yin et al., 2015), hepatocellular carcinoma (Zhuo et al., 2016) and osteosarcoma (Tian et al., 2015). Furthermore, it was observed that over-expression of MEG3 is significantly associated with gallbladder cancer prognosis (Liu et al., 2016a). Therefore, the results of these studies along with current meta-

analysis clearly support the clinical importance of MEG3 down-regulation as a prognostic biomarker of poor outcome in various cancers.

It should also be noted that lncRNA MEG3 not only act as a novel prognostic biomarker in cancer, but also as a potential therapeutic target. Many studies have demonstrated the anti-cancer effects of MEG3 lncRNA in various malignant tumors that appears to act via different mechanisms (Braconi et al., 2011; Huang et al., 2017b; Liu et al., 2016a; Sun et al., 2016; Zhang et al., 2017; Zhang et al., 2016b). In line with this, Zhang et al. showed that MEG3 functions as a tumor suppressor by reducing the level of miR-21-5p expression, resulting in the inhibition of tumor growth in cervical cancer (Zhang et al., 2016b). Liu and colleagues report that MEG3 could inhibit the proliferation of gallbladder cells and promote apoptosis, suggesting that MEG3 up-regulating could be a novel therapeutic strategy against gallbladder cancer progression (Liu et al., 2016a). Moreover, it has been shown that MEG3 inhibits cell growth and induces apoptosis in ESCC cells, mostly via activation of the endoplasmic reticulum stress pathway (Huang et al., 2017b). Furthermore, Zhang et al. reported that MEG3 suppresses BC cell growth, invasion, and tumor angiogenesis via down-regulation of AKT signaling pathway and hence may serve as a novel therapeutic target of BC (Zhang et al., 2017). Consistent with these finding, Braconi and colleagues have reported that aberrant expression of MEG3 may trigger apoptosis in HCC cell lines (Braconi et al., 2011). It has also been shown that the down-regulation of MEG3 induced activation of the Wnt/ β -catenin pathway in retinoblastoma cells and lung cancer cells (Gao and Lu, 2016; Xia et al., 2015).

Moreover, It has been established that MEG3 contributes to the pathogenesis of tumors through its interaction with p53 (Zhou et al., 2007), but the underlying mechanisms of MEG3 dysregulation has not been clarified. Sun et al. reported that overexpression of MEG3 in BC cells prevents the proliferation and invasion properties of tumor cells, by enhancing transcriptional activity of p53 on its target genes (Sun et al., 2016). P53 as a tumor suppressor involve in the regulation of many target genes, such as ARF, PTEN, p21, BAX, BRCA1 (Hermeking, 2012; Muller and Vousden, 2013). p53 expression produces p53 protein, which can inhibit cell division (Feng and Levine, 2010). MDM2, one of the E3 ubiquitin ligase

regulated the p53 protein level. It has been reported that aberrant regulation of MEG3 lead to reduced RNA and protein amount of MDM2 and increased p53 level. On the other hand, MEG3 motivates p53 activation through MDM2 down-expression (Lv et al., 2016). Moreover, MEG3 induced apoptosis of cancer cells by down-expression of the Bcl-2 protein and the over-expression of the Bax protein. Furthermore, MEG3 can activate caspase 3, an important mediator of the apoptotic cascade (Cohen, 1997; Lakhani et al., 2006; Lamkanfi et al., 2007) and cause G₀/G₁ arrest by down-expression of Cyclin D₁, a major regulator of G₁/S transition (Luo et al., 2015). Taken together, it seems that MEG3 can also serve as a potential novel therapeutic target to improve outcomes in cancer patients.

Our meta-analysis included 13 recently published manuscripts and comprised 1733 patients with 9 different cancer types. The combined HR revealed that a low expression of MEG3 is significantly associated with poor prognosis of patients with different types of cancer. Sub-group analysis of studies including eight studies of GI cancer patients and 2 studies of BC patients showed convincing evidence that increased expression of MEG3 is not significantly related to longer OS time. Due to limited number of studies for each cancer site, these conclusions require more prospective studies for validation.

There are several limitations in current meta-analysis. First, there was clear evidence of heterogeneity; second, most studies reported positive associations rather than negative results; and we only included English language manuscripts. Third, all the included studies were conducted within Chinese populations, which may have implications with respect to the general applicability of these findings. Fourth, there are inconsistencies about definition of cut-off values for the expression of MEG3 in different studies.

In conclusion, MEG3 appears to be an independent factor that plays a significant role in inhibition of cancer cell proliferation by regulating p53. However, the role of MEG3 in human cancer OS is still contentious in clinical settings. Thus, a meta-analysis was used as an approach to resolve this issue. Our results show that only in the pooled analysis, was there hallmark relationship between MEG3 expression and cancer survival. This is probably a consequence of the relatively small sample of studies so far undertaken. Taken together, it

seems that MEG3 can serve as a novel prognostic biomarker as well as a potential therapeutic target to improve outcomes in cancer patients.

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Figure legend

Figure 1. Literature research flow diagram.

Figure 2. Forest plot presenting the relationship between MEG3 expression and OS of all patients with different solid tumors (A). Funnel plot showing the relationship between MEG3 expression and OS of all patients with different solid tumors (B).

Figure 3. Forest plot demonstrating subgroup analysis of the relationship between MEG3 expression with OS in patients with GI (A) or breast cancer (B).